COMMENTARY ON CARDIOVASCULAR DISEASES

Analysis of the origin, development and therapy of cardiovascular diseases constitutes a major challenge.

In recent months, a committee of the American Heart Association and its Board of Directors announced their recognition that the statistical association between heavy cigarette smoking and increased mortality and morbidity from coronary heart disease did not prove a causal relationship. While we do not agree with all the other statements made in their report, we do think that the carefully delineated recommendation of the committee for "expanded biological and medical research...on the relationship of smoking to cardiovascular diseases" are worthy of reiteration.

A reading of these research recommendations makes plain that scientifically sound conclusions as to the relationship, if any, of smoking or other suspected factors to the etiology of cardiovascular diseases should be deferred until much of this proposed research has been conducted, and the results evaluated.

The areas where the American Heart Association particularly recommends research are:

(a) More and larger longitudinal epidemiologic studies of cigarette smoking in relation to coronary artery and other cardiovascular diseases.

(b) Possible correlations of smoking in various population groups with diet, physical activity, heredity, emotions, blood clotting, blood lipids, and other factors which may be or are known to be causally related to such manifestations of atherosclerosis as myocardial infarction and strokes.

(c) Effects of duration and intensity of smoking on the risk of developing coronary artery disease.

(d) Relationship of pre-clinical atherosclerotic lesions to smoking habits in individuals under 45 years of age.

(e) Effects of tobacco and the constituents of tobacco smoke on the heart and blood vessels of animals and humans and on such disease processes as experimental atherosclerosis.

(f) Studies on patients to determine the influence of smoking on known coronary artery disease and on intravascular clotting (thrombosis), including the effect of cessation of smoking on longevity and health in patients with established coronary artery disease.

(g) Studies of the differences between the effects of cigarette and pipe or cigar smoking, since the latter two apparently do not have a statistically significant association with cardiovascular disease.

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The Tobacco Industry Research Committee and others have sponsored continuing and expanding researches in many of these areas, as well as in other pertinent fields.

The list of areas needing "expanded biological and medical research" could be extended by substitution in turn of each of the suspected factors other than smoking. Undoubtedly, such research should and will be undertaken relating to each and all of these factors.

No effort will be made in this commentary to cover in detail the literature which deals with the more general aspects of cardiovascular abnormalities or pathology.*

Our discussion seeks to assist the Committee by commenting on some aspects of existing knowledge -- and gaps in that knowledge -- in this complicated field. It is by no means comprehensive, in large part because the work yet to be done precludes such treatment at this stage. It is largely limited to smoking but the comments are, in many instances, applicable to other suspected factors.

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* - Extensive material dealing with the following topics is available in the TIRC library:

General Systemic Effects of Tobacco
Peripheral Vascular Diseases
Blood and Circulation
The Heart and Coronary Vessels
Factors in Cardiovascular Disease: Heredity
Emotional
Stress
Diet
Physical Inactivity

Epidemiology

We will be glad to submit any or all such material or bibliographical lists as may be requested by the Committee.

A bibliographical project assisted financially by the TIRC culminated in publication of the monograph entitled, Tobacco, Experimental and Clinical Studies, A Comprehensive Account of the World Literature, by Drs. Larson, Haag and Silvette (Williams and Wilkins, 1961). Chapters 6, 18 and 20 are particularly relevant to the present subject.

Because of the availability of this comprehensive review, the material submitted here is confined mainly to recent publications, many of which have appeared since completion of the monograph.

A symposium was held by the New York Academy of Sciences on March 24, 25 and 26, 1960 on the Cardiovascular Effects of Nicotine and Smoking. Published in the monograph of that title by the Academy on September 27, 1960 were reviews of most of the studies sponsored directly by the Tobacco Industry Research Committee up to that time. (Annals of the New York Academy of Sciences, Vol. 90, Art. 1, pages 1-344, 1960.) A copy of this has been furnished to the Committee.

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Comments on the following general topics, together with some literature references, are attached:

I. Multifactorial Etiology

II. Epidemio-Statistical Principles

III. Pharmacology of Nicotine

IV. Initiating versus Developmental Influences

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I. MULTIFACTORIAL ETIOLOGY

Because of the problem of interrelationship, certain of the suspected factors other than smoking will be mentioned briefly. The objectives in doing so are:

(a) To emphasize the need for developing a perspective that will lead to the eventual evaluation of the various suspected factors as being independent, correlated, cumulative, antagonistic or synergistic agents in the origin and/or progressive development of cardiovascular disease.

(b) To indicate possible variables in connection with which smokers of various types and degrees may be contrasted with non-smokers or with those who have discontinued smoking for different periods of time.

Multifactorial Studies

Several multifactorial prospective studies, particularly those of the Framingham group, of the Albany group, of Stamler and of Oglesby Paul have endeavored to reach a profile description of the coronary-prone individual. For such purposes, it has been necessary to employ available clinical definitions of the various cardiovascular conditions, in order to relate incidence epidemiologically to constitutional and environmental factors. In general, the lack of autopsy data has been recognized as a serious handicap to precise description and classification.

Some degree of success has been attained in reaching a profile description. Hereditary factors seem to be quite generally recognized. Epidemiologically, a rather persistent association between prevailing high serum cholesterol levels and risk of developing cardiovascular disease has been reported. High prevailing blood pressures, overweight, cigarette smoking, left ventricular hypertrophy, low vital capacity, history of shortness of breath, history of peptic ulcer, history of chest discomfort, A-V nicking of the fundi, and heavy use of coffee have been reported also to show various degrees of association. Combinations of certain of these factors are associated with higher risk in some reports, but not in others.

Of course, no studies of this kind can be used alone to determine whether any one or any combination of the measured factors actually contributes causally to production of disease or whether they tend rather to reflect the existence of some constellation of more basic congenital predisposing characteristics which result in higher disease incidence. For example, voluntary cessation of cigarette smoking may itself reflect selective constitutional differences. The inevitable uncertainties inherent in these studies are recognized as being a severe handicap to design of effective preventive measures.

It is of interest that cigarette smoking does not appear to be associated with development of chronic angina. Since this disease is considered to be a consequence of general atherosclerotic narrowing of the coronary arteries, this lack of association has been interpreted as indicating

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that smoking probably does not contribute to progression of the atherosclerotic process. The association of cigarette smoking with mortality from cardiovascular disease, which nevertheless persists, is therefore difficult to interpret. The hypothesis of selective constitutional differences may present one possibility. Another hypothesis that has been advanced is that smoking may somehow be involved in the still obscure processes by which acute episodes are precipitated in persons with advanced underlying atherosclerotic disease.

Another puzzling observation is the great difference, epidemiologically, between cigarette smokers on the one hand and smokers of pipes and cigars on the other.

Diet

This is a controversial topic that has produced a voluminous literature.

There appears to be quite general agreement that lipid metabolism is somehow involved in the atherogenesis which underlies much cardiovascular disease. However, until a more definite pattern emerges which can successfully integrate such factors as the kinds and amounts of fats consumed, the inborn metabolic differences of individuals, physical activity in relation to amounts and kinds of food consumed and others, there appears to be little prospect of determining whether dietary factors and smoking habits are interrelated or of evaluating their relative significance, if any, in the etiology or aggravation of these diseases. (See reviews by Stamler, Keys and others.)

Therefore only a few excerpts from papers which may be of possible interest are appended.

Brontë-Stewart, studying reported differences in the relative incidence of ischemic heart disease among the three major ethnic groups of the Capetown area, has reported evidence of an association between smoking habits and habitual dietary fat intake. He has suggested that smoking may exercise an indirect influence by modifying food selection through effects on the taste sense. A subsidiary study by Brontë-Stewart's group has reported that smokers seem to show a diminished sensitivity to bitter and may have a relative preference for salty, spiced and high-fat foods. These latter observations have not yet been confirmed or generally accepted, but further taste-sensitivity studies in relation to smoking are being conducted at present by other investigators.

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Lack of Exercise

Lack of exercise is regarded by many authors as an important factor in development of heart disease. Several of these papers are mentioned below:

(a) Two independent studies of Alpine populations report independence of dietary, smoking and alcohol-use habits from incidence of cardiovascular disturbances. Their record in this respect was distinctly better than that of nearby urban inhabitants. The authors consider the difference in physical activity to be of real importance.

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A somewhat similar type of comparison was made between Finnish lumberjacks and the other male population of the same area. The lumberjacks (who tend to smoke more than the general population) were engaged in the greatest physical activity and had significantly fewer electrocardiographic changes indicating past myocardial ischemia.

(b) Four studies deal with comparisons between more and less active occupational groups in England or in the United States. Each study reaches the conclusion that the risk of cardiovascular disease is less in the more physically-active groups than in the less active.

(c) The relatively high risk of those engaged in sedentary occupations, independent of smoking habits is emphasized in two papers.

(d) The immediate effects of exercise in relation to smoking is reported in one paper. The authors conclude that "habitual smokers tended to show a faster adjustment to exercise and a faster rate of recovery than non-smokers."

Genetics

A. General Comments

In considering the genetic factors as one type of influence in etiology and/or progress of cardiovascular diseases, it is desirable to bear in mind certain possible characteristics of these factors and the effect of these upon their detection, identification and analysis.

First among the probable characteristics may be mentioned complexity. In any effect upon incidence or progress of cardiovascular diseases in adults it is almost certain the complex interaction between the genetic potentialities of the individual and his environmental experiences, both external and internal, will be involved. The direct, simple genetic control of adult response as indicated by classical mendelian results will be the very rare exception.

Far more frequent and more difficult of analysis will be the increased tendency to cardiovascular diseases as detected by higher correlation between disease in one or both parents and offspring or between siblings. Paul has shown an association between incidence of coronary disease in the offspring and early death of the father.

A paper by Böök states:

> "...in so far as metabolism is concerned people differ genetically as much as in physical traits... Looking at heredity and heart disease has taken us from congenital malformations to nutrition. What ties the diverse fields and many others together are the fundamental principles of biological variation..."

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McKusick, in discussing four major types of cardiovascular disease, states:

> "There is a clinical impression partially corroborated by statistical and genetic investigations, that heredity plays a role in...atherosclerosis, including coronary artery disease; hypertension, rheumatic fever, (and therefore rheumatic heart disease) and congenital malformations of the cardiovascular system."

B. Lipid Metabolism

Genetic factors in determining serum phospholipid levels and serum cholesterol levels are mentioned in two independent papers among those being submitted. A third paper reaches the interesting conclusion that hypercholesterolemic xanthomatosis is inherited by simple mendelian dominance. Since this condition may be a precursor of coronary artery disease, it is of potential significance.

McDonough et al., in a study of twins, clearly showed that genetic influences were operative in affecting variation in cholesterol level.

C. Hypertension and Atherosclerosis

There are several communications included on this subject from a genetic point of view.

Miall and Oldham find evidence that the arterial tension is a continuously variable characteristic and that relationship in arterial pressure between relatives and propositi indicated "graded and polygenic inheritance." Familial grouping of arterial hypertension and of atherosclerosis is also reported by Miasnikov. Perera, in discussing these diseases, states that there is a possibility that "...hereditary factors leading to variations in individual susceptibility may be all important."

Shanoff et al. studied 102 male survivors of myocardial infarction with atherosclerosis of the "essential type." Coronary heart disease was more prevalent in the parents and in the siblings, especially the brothers of the coronary patients. Smoking and alcohol consumption was similar in the coronary group and in the controls.

Sir Robert Platt differentiates between secondary hypertension, which he does not consider "in general hereditary," and essential hypertension, which he calls "a specific inherited disorder of middle age."

D. Multiple Factors

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Perhaps one of the most interesting and extensive series of studies is that of Dr. Caroline B. Thomas. In a number of papers covering work of a decade or more she has given a fairly comprehensive picture of a complex problem.

Thomas recognized that "identification of groups susceptible to coronary and hypertensive heart disease is necessary for...testing preventive measures." She has studied, in a population of medical students "hypercholesterol levels, overweight, hyperblood pressures, hyperheart rates, body build, hyperreactivity to colds and exercise."

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A definite genetic influence as measured by parent-offspring resemblance has been detected. Moreover, the subjects presumably predisposed to cardiovascular disease on the basis of family history as reflected by these factors, showed an increased tendency to be smokers.

She has also contrasted smokers and non-smokers among different blood groups and has found a significant difference in blood group distribution between white male smokers and non-smokers.

Emotional-Mental Stress

It may be argued that "mental" and "emotional" are not synonymous and that they should not be combined in any discussion of stress in relation to cardiovascular diseases.

It seems unnecessary to argue that matter in the present presentation. The material appended provides a sample of the sort of data that appear to justify the general concept that stress, or some constitutionally determined patterns of reaction to stress, whether emotional, mental or both are factors to be considered in the etiology and/or progressive course of cardiovascular disease.

Excerpts are appended related to the following:

A. Actual Biochemical Effects of Stress

Lipoid Metabolic Changes: These have been recorded, under stress of various sorts, by Hammartsen et al., Thomas et al., Wertlake et al., Cardon and Gordon, Dreyfuss and Czaczker, Drundy and Griffin, Rosenman et al., Kitchen, Cathey et al., and Wolf et al.

Hypertensive Changes or Symptoms: These were recorded following stress by Miasnikov, Lipman, and by Hokanson and Burgess.

Other Cardiovascular Changes: Stress is reported to shorten the recalcified plasma clotting time and increases plasma fibrinolytic activity according to Ogston et al.

In healthy male subjects, anger and anxiety increase the coronary blood flow according to Adsett et al.

Some of these effects have been shown to be related to the discharge of epinephrine from the adrenal gland.

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B. Relation of Stress to Cardiovascular Disease

Stress as a contributory factor to cardiovascular disease in general has been implicated in papers by Weiss et al., Sigler, Friedman et al., and Fisher.

Various arrhythmias and increased arterial pressure in patients with essential hypertension and in normals have followed stress according to Wolf. Congestive heart failure is connected with stress by Chambers and Reiser, while coronary heart disease is affected according to Russek, and to Pearson and Joyce.

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C. Relaxing Effects of Smoking

These effects of smoking are difficult to demonstrate by exact tests. It is, however, of possible interest that certain clinical investigators mention the subject.

As examples may be cited a paper by Conn and Kissane and three papers by Levy and his associates.

D. Smoking as a Reflection

The view that excessive smoking may be a reflection of the presence in certain types of individuals of increased predisposition to cardiovascular disease rather than acting as a cause of such diseases is held by some research workers.

Not many have explicitly stated this belief but Friedman and his associates are among those who have done so.

It is well to note, however, that the minor role assigned to smoking by the large number of workers to whom reference has been made in the consideration of stress indicates a very definite doubt in their minds as to whether smoking has significant etiological effects.

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II. EPIDEMIO-STATISTICAL PRINCIPLES

Non-Association of Smoking and Cardiovascular Disease

There are very definite differences of opinion among epidemio-statisticians as to whether smoking has any significant effect upon the origin or progress of cardiovascular disease.

The situation is complicated because of the very nature of the diseases themselves and because of existing variations in diagnosis and classifications.

In spite of this, however, it may be useful to cite several examples of studies in which evidence of no significant association between smoking and cardiovascular disease was obtained.

Luongo found no effects of smoking in a test group of 100 patients with coronary disease and 200 controls without coronary disease, in Los Angeles.

In England, Brown et al. examined 1062 men aged 60-69 and found that the prevalence of symptoms or signs of coronary disease was unrelated to smoking habits.

Pomeroy and White found "little difference" between heavy smokers and non-smokers in a follow-up study of 424 Harvard football players for 25-50 years.

Employees of tobacco companies are known to have a higher daily per capita consumption of cigarettes than that of the general population. Dorn and Baum, Haag and Hamner, and Cohen and Heimann showed that, among such employees, death rates from cardiovascular disease were either similar to or lower than that of the general population.

In Austria, Feiks found "no noticeable difference" as regards cigarette smoking habits between patients with infarcts and a control group.

Two studies on Indians are of interest. In Kenya, Charters and Arya found that immigrant Sikhs, who never smoke, had approximately the same incidence of ischemic heart disease as did Punjabis and Gujeratis among whom most Indian males over 25 years of age are smokers. Mathur showed no relation of smoking and coronary heart disease in 553 cases studied in Agra.

In Sweden, Malmcrona et al. studied 155 survivors of a series of 318 cases with myocardial infarction and found no significant effects of smoking.

Wilens and Plair report that among 989 consecutive autopsies on veterans (1958-61) the incidence of hearts with one or more infarcts did not "vary significantly" in "the various categories of smokers and non-smokers." They point out, however, that their findings "do not preclude the possibility that heart attacks...may be more severe clinically and more often fatal" in heavy cigarette smokers than in non-smokers.

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Cause and Effect Judgments

A considerable body of opinion exists which recognizes the usefulness of epidemio-statistical studies but emphasizes their inadequacy as a proof of cause and effect.

Heady, and Page comment on the danger of accepting statistical association as meaning cause and effect. As an example, they point out that among other things the closest correlation with cardiovascular diseases is the ownership of television sets.

The claim of statistical association in certain types of person or of behavior pattern as indication of a possibly important relationship is made by Friedman and by Ustoedt.

Heath, and Stamler, recognizing the confusion and complexities existing in efforts to unravel various suspected factors, urge caution in causal interpretations of any of them at present.

Two experienced scientists, one a clinician and the other an actuary, have made excellent summary statements of the justifiable attitude toward smoking as a causative factor in cardiovascular disease.

Irvine Page states, "one must be very careful in accepting such a relationship without experimental evidence," and Edward Lew, chief actuary for the Metropolitan Life Insurance Company, wrote in the same year:

> "A number of investigators have reported a high degree of association between death rates from heart disease and cigarette smoking... A high degree of statistical association does not necessarily imply that excessive cigarette smoking is a cause of coronary disease. The effect of smoking on existing coronary disease remains to be weighed as a factor in the rise of the death rate from this disease."

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Inadequacy of Death Certificates and Diagnoses

The weaknesses in the present diagnostic-death certificate procedure as an accurate quantitative measure of incidence and morbidity from the complex constitutional diseases is widely recognized. However, since this type of method is the easiest and most popular way of accumulating masses of records, these data become a very real factor in the analysis of the problem from a scientific point of view.

A few examples of papers dealing with this phase of the study of cardiovascular disease will therefore be appended.

Discussing the interpretation of cardiovascular-renal disease mortality statistics, Moriyama, Chief of Mortality Analysis Section, USPHS, found that, on the basis of comparisons between clinical and pathological records, the "diagnostic statements" are "relatively poor" and stated that "there should be a more general recognition that mortality data are not precise measures."

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Williams studied the reported incidence of death from coronary conditions in 3,557 death certificates in Pennsylvania and found an indicated incidence of one such death in every 3.9 reported. Upon screening these death certificates, the incidence was found to be one in every 7.2 deaths. As Williams states, "the death certificate can be a meaningless document as a source of information as to the cause of death."

Changed procedures in classification and in diagnosis affect greatly the data on mortality in terms of death certificate records according to Lew, Friedberg, and others.

In 1957, Zeman showed only 72.8% agreement between death certificate and autopsy in arteriosclerotic heart disease, and 59.5% agreement in death from vascular diseases of the central nervous system.

Allison et al. found that there was about a 14% error in positive diagnosis of myocardial infarction at the Boston City Hospital, but that 46% and 31% error was made in overlooking or questioning the occurrence of this condition.

Is There Any Real Increase In Cardiovascular Disease?

One of the most striking difficulties in studying the epidemiology of cardiovascular disease arises from the lack of adequate data on morbidity.

There are interesting and suggestive differences of opinion concerning the reality of reported changes in the incidence of cardiovascular disease. A few of these opinions are appended to give an idea of the various points of view.

Emerson stated that an apparent 60% increase in crude death rate, reported for heart disease in this country and Western Europe over a 35-year period, became "not more than about 10%" when correction is made for the aging population. He further stated that mortality rates for total cardiovascular-renal disease, when so corrected, have fallen approximately 33% since 1910.

Since 1950, Warren reports a 6% drop in death rates in men from 45-64 years old, but points out that this decrease is in the hypertension and cerebral hemorrhage groups while death rate from other coronary disease "went up slightly."

Some of the uncertain factors influencing records of incidence on which increases or decreases in death rates have been estimated are mentioned by Masters, who emphasizes the possibility of high incidence of coronary disease which has not yet reached the symptomatic stage, in young men.

Spain believes that "the recent increase in coronary atherosclerosis is absolute and considerable," but also recognizes many possible factors which may be involved, and exonerates smoking as a causative factor. Seeking to reconcile his data with those of Hammond and Horn, Spain speculates that smoking may still be guilty of having "some deleterious effect" on those already afflicted.

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Two papers more or less sum up some of the broad uncertainties which are innate in the present situation and which influence reliability of interpretations of increase or decrease of these diseases. One of these is by Mainland and the other by Isaac Starr who says, "it is my strong impression that arteriosclerotic heart disease is being written on death certificates of most elderly persons whose primary cause of death is either unknown or unclear to the attending physician" ... "diagnostic fashions change with time as well as with place."

We have previously submitted as a separate document, a paper by Lew entitled "Biostatistical Pitfalls in Studies of Arteriosclerotic Heart Disease." This paper presents a thorough discussion of this subject.

The evident discrepancy between the relatively stationary death rates from major cardiovascular diseases and the concurrent recorded increase in per capita cigarette smoking in the United States is a fact of significant importance. It does not support the theory that smoking is an important factor in either the etiology or in the progressive development of these diseases.

Hormonal Factors

There is a generally admitted difference between the sexes in their apparent susceptibility to cardiovascular diseases.

Some investigators consider this difference to be due directly to the sex hormones while others are inclined to associate it with the degree of stress and strain of modern living, and/or the response to that stress and strain which is commonly assumed to be different between men and women.

Ovarian failure is particularly emphasized by Cochran and Gwinup as a predisposing factor in development of atherosclerosis. Madigan found that the sex difference in susceptibility still persisted between two groups of Roman Catholic religious brotherhoods and sisterhoods engaged in educational work and subjected to essentially the same degree of stress and strain. Lilienfeld found the difference also to be independent of socio-economic group.

Rosenman and Meyer, however, contrasted the incidence of cardiovascular abnormalities in three groups of women differing in degree of competitive drive and stress. They found marked positive association with stress.

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It should be noted, however, that the two points of view concerning hormonal factors are not necessarily exclusive of one another. Stress may still be influential within different groups of either sex and yet the hormonal factors may be the chief source of different susceptibilities between the sexes.

It has never been seriously suggested (nor do any data support the supposition) that smoking differences can account for the observed differences between the sexes.

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Geographic Variation

As in epidemiological studies on all the other constitutional diseases, wide differences in reported incidence and distribution of cardiovascular diseases occurs between distinct geographic areas.

A sample of variation between areas and ethnic groups of the same city (Capetown) is given by Brontë-Stewart, who points out that smoking habits are similar throughout the area studied. Wide differences between metropolitan areas, some of them in close proximity, was cited by Enderline et al., and between states by Enderline and Stewart.

A general paper of interest, giving a broad discussion of geographic differences in medicine has been published by Sauer.

How different factors of environment are involved and how important variations in diagnostic and recording accuracy may be are still unknowns. So also are possible ethnic or behavior pattern differences.

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III. PHARMACOLOGY OF NICOTINE

There is a vast literature on this subject, which dates back into the early nineteenth century. Nicotine has a multiplicity of actions, which are highly dose-dependent. Overall responses may therefore appear paradoxical. The complexity of the responses and their dose dependency probably conduce to the expression of individual differences among human subjects, dependent on the relative reactivities of their various systems as determined by genetic factors as modified by life experience.

In low concentrations, nicotine has a stimulating action on certain chemoreceptors which initiate reflexes affecting many parts of the body. The most important of these are the receptors of the carotid and aortic bodies. Somewhat higher concentrations can stimulate both the sympathetic ganglia and the parasympathetic ganglia while still higher concentrations block or paralyze ganglionic transmission. Since sympathetic and parasympathetic nerves in general mediate opposite effects, these dual effects of nicotine can contribute to the appearance of paradoxical responses. The interpretation of the effects of nicotine is further complicated by the fact that it stimulates the release of epinephrine from the adrenal medulla and from other depots. The effects of this hormone on the circulation resemble in many respects those of nicotine itself.

A persistent and very practical problem is to appraise the significance of responses that human subjects may show from such nicotine absorption as occurs within the range of that normally received from ordinary tobacco use. Failure to so appraise the results of animal experiments conducted with higher dose ranges has led to many questionable extrapolations in the past.

Comroe has suggested the possibility that all the actions of nicotine inspired in tobacco smoke on the circulation and respiration may be brought about by the stimulating effect of nicotine on certain chemoreceptors, below the amounts having ganglionic action.

It must be noted also that all pharmacological effects of nicotine are very transient, because of the rapid metabolism and excretion of this alkaloid, and that no chronic or cumulative effects have been reported. On the other hand, some recent epidemiological studies have reported a higher death rate from several cardiovascular diseases among smokers, particularly cigarette smokers, as compared to non-smokers.

One problem is to attempt to determine which, if any, responses to smoking, harmless to normal individuals, might present a hazard to individuals with an already severely damaged cardiovascular system.

Kalow has described the net circulatory effects of nicotine on heart rate and blood pressure, despite the multiplicity of actions, as comparable to those of exercise: "The stimulation produced by smoking one cigarette is not more than that caused by a modest effort." One approach to the problem of patient management may therefore be consideration of his tolerance of "modest physical effort" while the search for any more relevant effect specific to nicotine is continued.

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Agress, employing a newer "vibrocardiographic" method of analyzing heart action, has compared responses to cigarette smoking with those following standardized exercise. He reports that the effects of smoking are equivalent to those from light exercise.

Within the context of the remarks above, abstracts of several cogent papers on "general pharmacology of nicotine" are appended.

Effects of Nicotine on
Coronary Artery Flow

Several studies on this subject have been sponsored by the Tobacco Industry Research Committee. These were made possible by the development of new techniques, first those employing catheterization of the coronary sinus and later those employing closed-chest methods. Similar studies have been made by investigators under other sponsorship.

Bargeron and collaborators showed by catheterization techniques that cigarette smoking in subjects without heart disease results in a significant increase in coronary blood flow and heart rate, and a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose.

Forte and collaborators made similar observations on anaesthetized dogs into which nicotine was infused.

Kien and collaborators confirmed these coronary flow observations on dogs but reported also a "brief but marked" increase in the oxygen saturation of venous blood following nicotine, which they regarded as reflecting a transient decline in cardiac oxygen utilization which was manifested also in the electrocardiogram.

Bellet and collaborators confirmed the lack of coronary vaso-constriction in dogs, following systemic nicotine administration, and proceeded to coronary artery injections of nicotine to elucidate direct cardiac effects independent of systemic changes. Parasympathomimetic, sympathomimetic and Bezold-Jarisch responses were observed.

An approach to the study of nicotine effects in coronary insufficiency has been made by Bellet and collaborators using dogs with coronary arterial ligation. Nicotine increased cardiac work markedly in both normal and ligated dogs. Coronary flow was increased by nicotine but the degree of increase was inversely related to the degree of coronary narrowing to the point of disappearance. Coronary vascular resistance and myocardial oxygen utilization declined during nicotine administration.

Bing and his collaborators have reported a series of studies contrasting the responses to nicotine by normal subjects and by patients with coronary disease. During cigarette smoking, both groups had significant acceleration of heart rate, a rise in arterial pressure (except in one coronary patient) and in left ventricular work but no significant change in coronary blood flow. Oxygen usage by the heart remained virtually unchanged. There was no evidence of ischemia in the coronary patients. The increased coronary flow, observed previously in normals after smoking, and the lack of such response in coronary artery disease patients, suggest that the latter may be limited in their capacities to expand coronary flow.

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Nicotine and the Peripheral Circulation

While this subject has been studied extensively in the past, considerable new knowledge has been obtained recently by more refined studies. Oppenheimer demonstrated long ago that a distinction must be drawn between influences that modify blood flow in the skin and those which affect the deeper circulation. Effects are often opposite on these two vascular beds.

Most recent investigations indicate that the inhalation of tobacco smoke reduces blood flow in the skin, especially of the toes. Wood has confirmed this response but has shown that in comparison, cooling the environment has a much more marked effect.

Conversely, smoking caused a moderate vasodilation in skeletal muscle (Reuf, Rottenstein et al.).

Eckstein, Coffman and their collaborators have measured the reactive hyperemia of the foot following venous occlusion. Smoking two cigarettes decreased this reactive hyperemia; on the other hand, cooling the environment produced a more consistent decrease.

Venous pressure-volume curves have been measured plethysmographically in the forearm of healthy men by Eckstein and collaborators. Intravenous nicotine administration produced venous constriction in nearly all, while venous pressure changes were not consistent.

Freund has reported a series of studies on the effects of sham and actual smoking on the peripheral circulation of normal subjects and of patients. Pulse rates increased after smoking but did not correlate with plethysmographic changes. Smoking generally produced significant fall in skin temperature, in radiosodium clearance and in venous oxygen saturation in normals, but such changes did not occur in patients with peripheral vascular disease. There were also marked individual variations in plethysmographic changes in both groups.

Because changes in the skin flow in the extremities may mask changes in skeletal muscle flow, Coffman and collaborators clinically studied the latter, as affected by smoking, by using the disappearance rate of a radioactive isotope from skeletal muscle of the calf. Fourteen of seventeen normal subjects showed an increase in skeletal nutritive blood flow during smoking, despite the usual decreases in skin temperature. An intact nervous supply to the limb is not necessary to the response since three of four sympathectomized limbs showed the same increased flow.

A review on the Effect of Nicotine and Tobacco on Muscle Function by Fischer, Silvette, Larson and Haag considers reported effects of nicotine in wide variety but concludes that human muscular efficiency is very much more influenced by psychological than by physiological factors and that so far as the ordinary smoker is concerned, there is little or no untoward effect of the practice on skeletal muscle function.

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Nicotine and the Central Nervous System

Schmitterlöw and Hansson have shown that when C^{14} tagged nicotine is injected intramuscularly into mice it is rapidly concentrated in the brain and spinal cord.

Domino has reported an action by nicotine on the ascending reticular activating system of the brain in dogs, which he believes is direct rather than mediated through epinephrine, nor-epinephrine, 5-hydroxytryptamine or vasopressin, though not all possibilities for mediation have been ruled out. This effect occurs with blood levels of nicotine such as are commonly achieved in tobacco use by man. At present rat studies are underway to explore the behavioral consequences of the effect. Very small subcutaneous doses of nicotine appear in preliminary studies, to increase slightly the learning rate for rats in a conditioned avoidance situation.

Nicotine and Serum Free Fatty Acids

Bellet and collaborators have reported that the smoking of two cigarettes by human subjects, including normals, heart cases and patients with other diagnoses, was followed by a brief elevation in serum free fatty acids. Since this is a well-known effect of epinephrine, it seems most likely that this response to smoking is mediated through epinephrine release by nicotine. Total serum cholesterol or triglycerides were not affected.

The response was not related to age, sex, previous smoking habits, type of cigarette or pre-smoking levels of free fatty acids. It was more marked in subjects with healed myocardial infarctions. Non-smoking controls subjected to idential venipuncture and other procedures also experienced a moderate but smaller increase in free fatty acids.

It has not been determined whether the exaggerated response of coronary patients is a result of their disease or reflects a pre-existing hyper-reactivity to stress.

Whether such transient free fatty acid elevations, occurring frequently, could influence the atherosclerotic process is a matter of speculation; the animal experiments superimposing long-term nicotine administration upon atherogenic diets do not lend much support to such a conjecture. (See Topic IV.)

Immunological Aspects of Tobacco Use

The question was raised long ago whether the "purely pharmacological" effects of nicotine or smoking might be complicated by superimposed responses due to allergic hypersensitivities in some individuals.

A general critical review of the subject has been published by Silvette, Larson and Haag, which concludes that experimental work on immunology to tobacco has been fragmentary and that a complete classic immunological study of tobacco is urgently required, not only for its own sake but as a basis for evaluating concepts of tobacco's possible role as an etiological agent in disease.

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Such investigations have been undertaken by Sulzberger, Redisch, Fontana, and their collaborators. In a series of papers they report that patients who have symptoms which might be attributed to smoking, such as cough or disturbance of the peripheral circulation, show a higher incidence of skin sensitivity to tobacco extracts than do others. These studies continue.

Circulatory Effects of Pipe and Cigar Smoking and of Tobacco Chewing

Limited studies by Simon and collaborators have shown that the circulatory effects of pipe and cigar smoking and of tobacco chewing are similar in nature to those produced by cigarette smoking and hence are probably attributable to nicotine absorption. Transient increases in pulse rates and in systolic and diastolic blood pressures generally occurred, while a drop in skin temperatures of fingers and toes was general. Ballistocardiograms were altered in many of the older subjects but usually not in the younger ones.

According to Simon, the effects of cigar and pipe smoking were generally less marked than those of cigarette smoking or tobacco chewing.

Larson, however, has summarized the observations of several investigators on nicotine absorption from various forms of tobacco use. Some have concluded that more nicotine is absorbed from cigar smoke, even without inhaling, than from cigarette smoke. Absorption is related to moisture content of the cigar and alkalinity of the smoke.

These observations seem especially important for consideration in relation to the marked differences found in epidemiologic studies with respect to the reported low cardiovascular death rates among pipe and cigar smokers as compared to those among cigarette smokers. It appears doubtful whether differences in measurable cardiovascular responses to these various forms of tobacco use are adequate to explain such marked epidemiological differences.

Studies currently underway are attempting to refine the measurement of the relative nicotine absorption from actual cigarette, cigar and pipe smoking.

Experiments on the effects of nicotine administration to animals on atherogenic diets are discussed under Topic IV.

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IV. INITIATING VERSUS DEVELOPMENTAL INFLUENCES

General Comments

It is obviously difficult to separate influences on the initiation of cardiovascular diseases and those which affect the development of such diseases once they are established.

This is especially true where recognition and classification of the disease occur only after other symptoms exist, as is usually the case.

As might be expected, there is no hard and fast rule or universally consistent clinical opinion on this matter. It is clear that individuals differ in response to smoking and to their deprivation from the habit.

Further research may conceivably indicate that a sufficiently high percentage of those with established degrees of cardiovascular disorders will react so unfavorably to smoking as to justify medical advice on certain courses of restrictive action. This, however, is properly a matter of relationship between the individual doctor and his patient. The desired situation is one which will involve as broad and comprehensive knowledge as can possibly be acquired to guide the profession in the light of its clinical experience.

The references appended will present opinions which are based on such experience. They should be considered as being contributory rather than conclusive and as being selected for purposes of comparison.

The important point is that more refined and sophisticated longitudinal studies of controlled populations of apparently normal individuals are sorely needed. These should aid in refining our recognition of departures from normalcy which represent the earliest evidence of the diseases under study and which, therefore, may be closely connected with their origin.

Similarly, manipulable populations of patients with established early cardiovascular diseases should provide material for more sophisticated clinical studies of factors which may influence the progress and course of these diseases.

Until such studies are organized and bear fruit we shall have to be content with a type of evidence which leaves doubt as to whether we are dealing with factors which influence origin alone, progressive development alone, or both.

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Ocular, Cerebral and Other Peripheral Circulation

According to Bettman, Fellows, et al., the effect of cigarette smoking on intraocular blood volume in man is not known. They have, therefore, used animals for experimentation.

If the cigarette was smoked at the normal rate there was no effect. If it was smoked rapidly there was a significant rise in intraocular volume. Denicotinized cigarettes gave generally similar results.

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In one rare arterial disease (thromboangiitis obliterans-arteriosclerosis obliterans) prognosis is improved (Boake and Barnet) by abstinence from tobacco. In atherosclerotic patients with intermittent claudication, there was no effect of smoking on the blood flow of the calf or foot. Abramson found no evidence that smoking affected progression of this disease. Selvaag et al. report similar results in Norway.

Hypertension

There is little evidence that smoking causes hypertension.

Actually D'Alonzo found that in employees of the E. I. DuPont de Nemours and Co. there was a higher prevalence of hypertension in non-smokers than in smokers. Hines finds no effect of smoking on the resting blood pressure. Similar results are reported by Hitchens.

Lower prevailing levels of blood pressures in smokers as compared with non-smokers have been reported by a number of investigators. Among these may be mentioned two papers by Brown et al. in England; a paper by Orma et al. and one by Karvonen, Orma et al. in Finland; and two by Blackburn et al. in the United States.

Cholesterol Levels

This is of course a subject on which there is a voluminous literature. According to various authors cholesterol levels appear to be affected by a number of factors such as diet, heredity, age, sex, stress and smoking.

Sufficiently well-planned and sophisticated clinical studies to analyze these variables or even to establish an adequate baseline of "normalcy" for range of cholesterol levels by age and sex are conspicuous by their absence.

Since there is no apparent consistent relationship between amount of smoking (Konttinen et al., Orma et al., Page et al.) and changes in cholesterol level, it would seem that no final conclusions are wise at this time.

On the other hand, there is sufficient evidence of a relationship between smoking and cholesterol level in certain individuals and in certain groups to offer a most intriguing field for further studies. For example, could the type and/or the degree of change in cholesterol levels be better analyzed by the use of smoking vs. non-smoking as a possible differential factor during the lifetime of various individuals observed under established and controlled conditions? Might not such observations help to analyze some of the individual host responses to the different factors which influence cardiovascular diseases?

Rather than over-organize the reports of research in the field of cholesterol levels, there are included references to and excerpts from a number of papers not specifically mentioned in this brief discussion, and yet of possible interest in connection with it.

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Atherosclerosis

Studies on the possible relation between smoking and atherosclerosis have been included in several of the groups of excerpts which are being forwarded.

It will be well to repeat the recommendation that evidence for or against etiological effects should be carefully distinguished from that bearing on progress of the already established diseases. Both aspects are important but their implications may be quite distinct and different in evaluating the potentialities and form of action of any suspected agent of habit such as smoking.

In this connection, Baltin comments on aggravation of coronary disease and Calataynd et al. on factors in its origin, in a population of Trappist monks.

As a matter of possible interest, a suggestion that density of population among the birds and mammals in the Philadelphia Zoological Gardens has been the main factor in a marked increase in coronary disease recorded at autopsy has been made by Ratcliffe. Although obviously smoking habits can be ignored, the possible bearing of this theory on human urbanization or overcrowding is worth mention in passing.

Animal Experiments Involving Nicotine Administration

The question whether repetitive small absorptions of nicotine, in view of its rapid elimination and metabolism, can produce any persisting effects, has been mentioned elsewhere. Several animal investigations have been conducted with a view to determining whether superposition of nicotine administration upon an atherogenic diet would modify or accelerate the development of arterial disease.

Wenzel has reported such studies on rabbits and hens, with use of high cholesterol diets to which graded doses of nicotine were added up to the "equivalent of two packs of cigarettes daily." The nicotine addition did not affect body weight, serum cholesterol levels, lipid phosphorus or gross aortic atherosclerosis. Electrocardiographic changes under ergonovine stress, were at first regarded as indicating more extensive pathologic changes. However, omission of ergonovine use in stress-testing the animals in vivo, virtually eliminated any anatomic difference between nicotine-treated and untreated animals, observable on autopsy. Hence the results appear to be equivocal.

Later experiments by Wenzel are reported as showing no effect of nicotine administration upon plasma cholesterol, lipid phosphorus or c/p ratios at higher cholesterol administration levels, but a significant increase by nicotine of these plasma components when dietary cholesterol was relatively low.

Because of the artificial nature of these rabbit experiments, and the doubtful analogy between atherosclerosis in man and such induced atherosclerosis in rodents, the interpretation of these results in terms of human experience is difficult.

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Travell and collaborators have shown that the normal enhancement by nicotine, of coronary artery blood flow in the isolated rabbit heart is not found in atherosclerotic rabbit hearts. A similar difference in the effects of norepinephrine was also observed.

Bellet and collaborators have reported that daily intramuscular injections of nicotine bitartrate, in a delayed absorption medium, into mongrel dogs was followed by a gradual increase in mean serum cholesterol levels, which attained a peak at the end of four weeks and was maintained for two more. There was no change in mean serum triglycerides.

Haag and collaborators have subjected weanling rats to cigarette smoke inhalation at half hour intervals, fourteen times a day for practically their entire life span, with two groups of controls. The smoked animals had the same average life span as controls, slightly lesser weight and the same prevailing blood pressures during non-exposure periods despite brief elevations in blood pressure immediately after smoking. The authors point out "the need for writers in this field to describe in sufficient detail the materials and techniques employed in their work to allow reasonable comparisons with other animal studies of similar nature, and with the conditions existing in human smoking."

Angina

Most authors agree that smoking is rarely, if ever, a precipitating factor in angina pectoris.

Conn and Kissane (1958) and Green and Borousch (1960) as well as Master (1956) all recommend a discriminatory point of view based upon study of the individual angina patient as the proper determiner of the nature of advice to be given him.

Buerger's Disease - Raynaud's Disease

In Raynaud's disease, restriction of tobacco does not appear to influence morbidity according to Gifford (1958). There is some evidence according to Peacock (1958) that mental stress -- at times associated with menopause or childbirth -- is an etiological factor in 50% of 42 cases. In the other 21 cases "no such etiological factors could be detected." Smoking is not mentioned.

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It may also be noted that Barnett and Boake (1960) observed no consistent change in blood flow of the calf in legs of six adult males affected by atherosclerosis.

An abstract by Abramson (1963) of a recent book on Buerger's Disease by DeBakey and Cohen reviewing World War II cases, states that "the relationship between smoking and the etiology of the disease was not sufficiently clearcut to be conclusive." It further mentions that "the study did not support the impression that abstinence from smoking caused amelioration of symptoms or a decrease in the necessity for amputation."

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In recent years there has been some debate as to whether Buerger's Disease is really a clinical entity distinct from peripheral vascular atherosclerosis. McKusick, with the aid of a Tobacco Industry Research Committee grant, has made a new study of this disease among young men in an Oriental country, where it is relatively more prevalent than in the United States, and has concluded that the syndrome as encountered there is distinct from generalized atherosclerosis or embolism of the peripheral vasculature. While all the sixty-two patients he observed were smokers, the study suggested strongly that the etiology and pathogenesis of the disease are probably complex and indicated that it still remains to be proved whether the essential lesion is truly an angiitis.

Miscellaneous Specific Relationships

Bing and his associates have, as previously mentioned, studied smoking and coronary blood flow, myocardial oxygen consumption, cardiac output and ischemia in normal patients and in those with coronary disease. Their results indicate no seriously deleterious effects but should be evaluated by firsthand study of the papers.

Freund (1957) shows no change in arterial or venous lactic acid, and Rehder and Roth (1959) no rise in the level of fasting blood sugar or in epinephrine-like substances of venous blood following smoking.

Bellet and collaborators have reported that nicotine infusion into dogs produces an increase in the fibrinolytic activity of their blood plasma. Human subjects are now being studied similarly.

No deleterious effect on ascorbic acid metabolism following smoking could be found by Taber and Larson (1962) in contrast to reports by McCormick.

Coagulability of blood was not affected by smoking according to Blackburn et al. (1959).

Davidge (1955), having studied 92 consecutive cases of myocardial infarction, stated, "there appears to be no relationship between the use of cigarettes and the occurrence of mortality" from that disease.

A conservative evaluation of smoking was made by Hunt (1956) who said, "it is hard to believe that smoking in moderation always makes coronary disease worse." Ellis and Hancock (1957) believe that "a physician should evaluate very carefully how important it is to restrict (by forbidding smoking) the happiness of a patient (coronary artery disease) who is already limited in so many ways."

Keys (1955) is much more assertive. He states, "I believe there is already evidence at hand to disprove the hypothesis that smoking has an important primary effect in the development of coronary heart disease;" and Hellerstein and Ford (1957), in a paper on rehabilitation of the cardiac patient, say that "the categorical denial of tobacco to all patients must be condemned vigorously... Most patients with heart disease can smoke safely without apparent harm."

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Source: https://www.industrydocuments.ucsf.edu/docs/ymk0068